Serial No.: 09/709,045
Filed: November 10, 2000
AMENDMENT

Remarks

Amendments to the Specification

Page 1, line 23, has been amended to insert a "", before granulocyte stimulating factor.

Page 6, line 4, the abbreviation of TNFR has been corrected.

Rejection under 35 U.S.C. 103

Claims 1-3, 6, 8-11, and 17-22 were rejected under 35 U.S.C. 103(a) as obvious over Selinsky, et al., Immunology 94(1):88-93 (1998) in combination with Van Zee, et al., Proc. Natl. Acad. Sci. USA (1992) in view of U.S. Patent No. 4,708,713 to Lentz and U.S. Patent No. 6,017,527. Claim 5 was rejected under 35 U.S.C. 103 over Selinsky, Van Zee, Lentz, Maraskovsky and Feinman, et al., J. Immunol. 138:635 (1987). Claim 10 was rejected under 35 U.S.C. 103 as obvious over Selinsky, Van Zee, Lentz, Maraskovsky, and Goodman. These rejections are respectfully traversed.

Lentz

Lentz describes removal of a large number of proteins using a filter. The only selectivity is by virtue of the molecular weight cutoff of the filter, which is approximately 200,000. ALL proteins in the plasma with the possible exception of some IgM will pass through a filter with a cutoff of 200,000. Therefore the limitations of claims 1-5, 8, 12 and 20 are not met.

Assuming the examiner meant to make a rejection under 35 U.S.C. 103, Selinsky does not make up for the deficiency of Lentz. Lentz teaches away from the selective removal of soluble cytokine receptor molecules. **Lentz states that the immune inhibitor which is being removed is believed to be a high molecular weight**

compound, not a soluble cytokine inhibitor such as soluble TNF receptor, which has a significantly lower molecular weight. Moreover, Lentz clearly does not know what the inhibitor(s) are, indicating that there are more than one inhibitor. In summary, Lentz teaches one of ordinary skill in the art that (1) the inhibitors are high molecular weight proteins and (2) there are more than one inhibitors involved in immunosuppression of the anti-tumor response.

Selinsky

Selinksky describes an experiment to correlate the levels of soluble tissue necrosis factor receptor ("sTNFR") with tumor burden. This in no way makes obvious the removal of sTNFR to treat tumors or other disorders. The standard under 35 U.S.C. 103 is whether the prior art leads one of ordinary skill in the art to combine the prior art as applicant has done, ***with a reasonable expectation of success.***

The prior art at the time this application was filed in May 1998, was that there were a number of tumor markers that correlated with tumor burden. The most well known include the prostate specific antigen ("PSA") and carcinoembryonic antigen ("CEA"). Studies had been conducted to remove both PSA and CEA, with the hope of decreasing tumor burden. Neither had been effective. Therefore, one skilled in the art would have had noexpectation of success that removal of a soluble cytokine receptor such as sTNFR would be effective.

Indeed, this is clearly the opinion shared by the authors of the paper. Enclosed is a copy of the Declaration under 37 C.F.R. 1.132 filed in U.S.S.N. 09/444,144, which subsequently issued as U.S. Patent No. 6,379,708 to Howell, et al. The examiner's

attention is drawn to pages 2-3 of the declaration, discussing first the Lentz patent and then the Selinksky paper. As the authors of the Selinsky paper noted:

"It is submitted that, although the statement in Selinsky et al. may cause one of skill in the art to consider how to antagonize or remove sTNFR1 *in situ*, such a statement is merely an invitation to experimentation and opens the door for one of skill in the art to consider a wide range of possible approaches. Indeed, Selinsky et al. provides absolutely no guidance as to how one of skill in the art would go about such a task, but rather generally state that the "therapeutic utility of manipulating sTNFRI levels *in vitro* has been demonstrated" and that "sTNFRI effectively inhibits immune responses *in vivo* and ...its modulation is a legitimate therapeutica avenue." It is submitted that one of skill in the art, when presented with an invitation to manipulate the effects of a soluble protein, would look to a variety of conventional approaches to remove or manipulate the effects of that soluble protein *in vivo*, because such approaches are the most clinically desirable means of treating a patient."

Van Zee

Van Zee merely reports that soluble receptors for TNF are present during inflammation and that excessive TNF present during the inflammation can be neutralized by binding to soluble TNF receptors.

This reference therefore ***teaches away from what is claimed.*** Van Zee teaches that one can decrease inflammation using soluble TNFR to TNF. Applicant claims a method of ***increasing inflammation and the immune response against tumors by removing sTNFR.***

Maraskovsky

Maraskovsky does teach that one can use an antibody column to remove materials from the blood. There is no teaching that it can be used to remove cytokine inhibitors to kill tumor cells.

For the same reasons that the examiner allowed the claims in the Howell patent over the combination of Lentz and Selinsky, so are the claims in this application allowable over Selinksky, Van Zee, Lentz, and Maraskovsky.

Feinman

Feinman does not make up for the deficiencies of the references discussed above. Feinman is not drawn to an *in vivo* situation, nor to treatment of tumor cells. Numerous studies have failed to demonstrate that interferon is useful in treating cancer.

Goodman

The examiner's characterization of the claimed method is inaccurate. The claims do not recite treating whole blood, but encompass treating whole blood or plasma. As described in the application, the blood is collected then separated into red cells and plasma, the plasma passed over the immunoaffinity column, then the red cells recombined with the plasma and the blood returned to the patient.

Goodman discloses making humanized antibodies. This does not make up for the deficiencies of the other references, however. Moreover, there is no motivation to use humanized antibodies, since these are immobilized, not administered to a patient.

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Proposed Amendment

Claims 17-22 have been added, which essentially correspond to U.S. Patent No. 6,379,708 to Howell, et al. This application claims priority to U.S.S.N. 09/083,307 filed May 22, 1998, before the earliest filing date of the Howell patent.

A proposed count is:

A method of enhancing an immune response in a patient comprising:

a. obtaining whole blood from the patient;

b. separating out the plasma;

c. contacting the plasma with antibody specifically binding to a targeted immune system inhibitor;

d. removing the inhibitor bound to the antibody from the plasma; and

e. returning the antibody-contacted plasma to the patient.

The basis for the claims is indicated in the claims as shown below in bold. The basis as found in Applicant's May 22, 1998, application is also shown below in italics.

17. A method of enhancing an immune response in a patient **(page 1, lines 6-7)** comprising:

a. obtaining whole blood from the patient **(page 18, lines 4-8)**; *(page 6)*

b. separating out the plasma. **(page 18, lines 7-8)**; *(page 6)*

c. contacting the plasma with antibody specifically binding to a targeted immune system inhibitor **(page 18, lines 8-11; page 6, lines 1-7)**; *(page 11, lines 23-26)*

d. removing the inhibitor bound to the antibody from the plasma **(page 18, line 8-11)**; *(page 11, lines 23-26)* and

e. returning the antibody-contacted plasma to the patient. **(page 18, lines 11-15).** *(page 7)*

18. The method of claim 17, wherein the antibody is immobilized in a solid support or membrane. **(page 9, lines 1-5)** *(page 11, lines 27-28)*

19. The method of claim 17, wherein the antibody is recombinant or a binding fragment. **(page 6, lines 18-20)**. *(page 11, lines 24-26)*

20. The method of claim 17, wherein the antibody is a mixture of antibodies immunoreactive with the targeted immune system inhibitor. **(page 6, line 27)** *(page 11, lines 22-29)*

21. The method of claim 17, wherein the patient is human. **(page 6, line 26)**. *(examples)*

22. The method of claim 17 wherein the targeted immune system inhibitor is selected from the group consisting of soluble receptors for tumor necrosis factors alpha and beta. *(page 11, lines 22-29)*

Double Patenting Rejection

As described by Chisum, "[d]ouble patenting is concerned with attempts to claim the same or related subject matter twice. Thus, the standard for comparison for the second patent is what was claimed in the first patent, not what was disclosed in the specification of the first patent." *Chisum*, 3:9.03[1][a]. "[A]n obviousness-type double patenting analysis entails two-steps." Eli Lilly & Co. v. Barr Laboratories, Inc., 251 F.3d 955, 58 U.S.P.Q.2d 1865 (Fed. Cir. 2001). First, one compares the later claim on the earlier claim to determine the differences. Second, one determines whether the differences in subject matter between the two claims demonstrates that the claims are patentably distinct. Id., *see* M.P.E.P. § 804, III (The rejection "must rely on a comparison **with the claims** in an issued or to be issued patent,...") (emphasis added). The Examiner failed to properly apply this standard of analysis.

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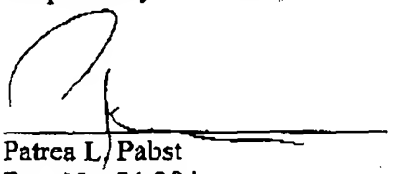
The claims in U.S. Patent No. 6,231,536 were interpreted by the examiner as requiring removal of the soluble tissue necrosis factor receptor using a molecular weight exclusion. There is nothing in such an interpretation that would make obvious the method as currently claimed. To the extent this rejection is maintained, it is respectfully requested that a final determination not be made until the outcome of the above-requested interference becomes available.

Allowance of claims 1-3, 5, 6, 8-11 and 17-22 and declaration of an interference with U.S. patent No. 6,379,708 is respectfully requested.

Respectfully submitted,



Patrea L. Pabst
Reg. No. 31,284

Date: October 29, 2003
HOLLAND & KNIGHT LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
(404) 817-8473
(404) 817-8588 (Fax)

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CERTIFICATE OF FACSIMILE TRANSMITTAL

I hereby certify that this correspondence and any document referred to as being included therein is being facsimile transmitted to the Patent and Trademark Office on October 29, 2003.

Patrea Pabst

METHOD AND SYSTEM TO REMOVE CYTOKINE INHIBITOR IN PATIENTS

Background of the Invention

The present invention is generally in the field of enhancing an immune response, and particularly relates to the removal of TNF inhibitors in a patient, such as a cancer patient, to promote inflammation and thereby induce remission of the cancer.

This application claims priority to U.S.S.N. 60/164,695, filed November 10, 1999.

Conventional cancer therapy is based on the use of drugs and/or radiation which kills replicating cells, hopefully faster than the agents kill the patient's normal cells. Surgery is used to reduce tumor bulk, but has little impact once the cancer has metastasized. Radiation is effective only in a localized area.

The treatments can in themselves kill the patient, in the absence of maintenance therapy. For example, for some types of cancer, bone marrow transplants have been used to maintain the patient following treatment with otherwise fatal amounts of chemotherapy. Efficacy has not been proven for treatment of solid tumors, however. "Cocktails" of different chemotherapeutic agents and combinations of very high doses of chemotherapy with restorative agents, for example, granulocyte macrophage colony stimulating factor ("GM-CSF"), erythropoietin, thrombopoetin, granulocyte stimulating factor, ("G-CSF"), macrophage colony stimulating factor ("M-CSF") and stem cell factor ("SCF") to restore platelet and white cell levels, have been used to treat aggressive cancers. Even with the supportive or restrictive therapy, side effects are severe.

such as a virus like HIV or parasite. The neutralizing agent is typically an antibody reactive with the receptor. the antibodies will typically be reactive with both the soluble and immobilized forms of the receptor. These include soluble tumor necrosis factor receptor ("sRTNF-R"), soluble interleukin-2 receptor ("sIL-2R"), soluble interleukin-1 receptor ("sIL-1R"), soluble interleukin-6 receptor ("sIL-6R"), or soluble interferon-gamma receptor ("sIFN-gammaR"). The advantage of selective removal or neutralization is that the same beneficial effect is obtained in treatment of the disorder but the treatment is much less expensive and safer since exogenous plasma or albumin does not have to be administered to the patient when there is selective removal, as in the case of ultrapheresis and the cytotoxic effects of radiation and chemotherapy are avoided.

The receptors can be removed by binding to the cytokine, an epitope thereof, or an antibody to the receptor. The antibodies to the receptors can be immobilized in a filter, in a column, or using other standard techniques for binding reactions to remove proteins from the blood or plasma of a patient, or administered directly to the patient in a suitable pharmaceutically acceptable carrier such as saline. As used herein, antibody refers to antibody, or antibody fragments (single chain, recombinant, or humanized), immunoreactive against the receptor molecules. In the most preferred embodiment, the antibody is reactive with the carboxy-terminus of the shed receptor molecules, thereby avoid concerns with signal transduction by the receptor is still present on the cell surface.

Antibodies can be obtained from various commercial sources such as Genzyme Pharmaceuticals. These are preferably humanized for direct administration to a human, but may be of animal origin if immobilized in an extracorporeal device. Antibodies may be monoclonal or polyclonal. The